UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/931,375	08/17/2001	Matthew L. Warman	38464-0004	1602

24024 7590 06/12/2006

CALFEE HALTER & GRISWOLD, LLP
800 SUPERIOR AVENUE
SUITE 1400
CLEVELAND, OH 44114

EXAMINER	
SEHARASEYON, JEGATHEESAN	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 06/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/931,375	WARMAN ET AL.	
	Examin r	Art Unit	
	Jegatheesan Seharaseyon, Ph.D	1647	

-- The MAILING DATE of this communication appears on the cover she t with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8,9,30 and 32-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8,9,30 and 32-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/30/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/30/2006 has been entered. An action on the RCE follows.

2. Claims 30, 35 and 36 have been amended. Therefore claims 8, 9, 30 and 32-38 are pending and under consideration.

3. The text of those sections of Title 35, U. S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

4. The information disclosure statement filed 3/30/06 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

5. Applicants amendments have necessitated the withdrawal of the pending claim objections.

Claim R jections - 35 USC § 112, second paragraph, withdrawn

6. The rejection of claim 35 under 35 USC § 112, second paragraph, as antecedent basis is withdrawn because of Applicants amendments.

Claim Rejections - 35 USC § 103, maintained

7. The rejection of claims 8, 9, 30, 32, 37 and 38 under 35 U.S.C. 103(a) as being unpatentable over Carulli et al. (U. S. Patent NO. 6, 780, 609) and Dong et al. (1998, Ref B06 in PTO1449 of 10/15/02) in view of Tamai et al. (2000, Ref A24 in PTO1449 of 5/1/02) is maintained. In addition, claims 33 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carulli et al. and Dong et al. in view of Tamai et al. and Opperman et al. is maintained. Further, claims 35 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carulli et al. and Dong et al. in view of Tamai et al. further in view of Wang et al. and Hughes et al. is maintained.

Applicants are arguing that Tamai et al. do not disclose that LRP5 is induced by Wnt signaling. In addition, Applicants contend that Tamai et al. have not drawn any conclusions regarding LRP5. Applicants further contend that Tamai et al. do not tell an artisan whether LRP5 protein is involved in the Tamai model of Wnt/β-catenin signaling. Further, Applicants discuss extensively the various mechanisms involved in the Wnt signaling pathway (see pages 6-7) and conclude that Tamai et al. do not teach or suggest that LRP5 is a Wnt ligand or a Wnt co-receptor, or even that Wnt is an effector of LRP5. Thus, it is concluded that the Tamai et al. disclosure, alone or in combination with Caurlli et al. and

Dong et al., does not make claims obvious. Further Applicants discuss the extensive experiments conducted on LRP6 (page 7). These arguments have been fully considered but not fond to be persuasive.

The claims of the instant invention are drawn to the administration/ providing of a ligand that regulates the bone strength and mineralization by acting on bone density regulating transmembrane receptor. Tamai et al. on page 531 set out to study LRP5/LRP6 involvement in Wnt signaling (see Figure 1 also). Figure 1a clearly shows the axis duplication in the presence of Wnt. As conceded by the Applicants (page 6, 3rd paragraph of the response) Tamai et al do teach that "Although LRP5 alone did not induce axes, co-injecting LRP5 and Wnt-5a did". Thus, providing a ligand (Wnt) to regulate the LRP5 (the transmembrane receptor) meeting the limitations of the instant claims because "Only a reason, suggestion or motivation need appear in the cited prior art in order to combine references under 35 U.S.C. 103. *Pro Mold Tool Col. v. Great Lakes Plastics, Inc.,* 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996)". Therefore, Tamai et al. teach the regulation of LRP5 a BSMR receptor by Wnt-5a ligand. Although, Applicants discuss extensively the experiments conducted by Tamai et al. on LRP6 and are comparing them to LRP5 (pages 7-8), the teachings clearly disclose that Wnt-5a along with LRP5 induce axes. It is noted that in considering the disclosure of a reference, it is proper to take into account not only specific teaching of the reference but also the inferences which one skilled in the art would be reasonably be expected to draw therefrom. *In re Preda*, 401 F.2d 825, 159 USPQ 342, 344 (CCPA 1968).

Applicants argue that Carulli et al., nor Dong et al. or Tamai et al. alone nor in combination teach or suggest that BSMR is a receptor for Wnt because Carulli et al. does not identify any molecules that bind BSMR in bone forming cells (page 9). This not found to be persuasive because as indicated in the Office Action dated 3/18/05 paragraph 9a, Carulli et al. reference was provided to teach that Zmax1 or HBM protein (similar to BSMR of the instant invention, see Office Action of 3/18/05 for the differences) was involved in the regulation of bone strength and mineralization. It also was provided to show the increase in alkaline phosphatase. It is not necessary that the claimed invention be expressly suggested in any one or all of the references to justify combining their teachings; rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. *In re Keller,* 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

Ligands capable of regulating BSMR are taught in Tamai et al which has been discussed above and in the Office Action dated 10/26/05 on pages 3-4. Therefore, combining the teachings of Carulli et al., Dong et al. and Tamai et al. one of skilled in the art would arrive at the limitations of claims 8 and 30 because *In re Kerkhoven* (205 USPQ 1069, CCPA 1980) summarizes:

> "It is *prima facie* obvious to combine two compositions each of which is taught by prior art to be useful for the same purpose in order to form a combination that is to be used for the very same purpose: the idea of combining them flows logically from their having been individually taught in the prior art."

Applicants also argue that, the claims 9, 32, 37 and 38 that depend from claims 8 or 30 are also not obvious. This not found to be persuasive for reasons

set forth above. Applicants also assert that neither Opperman et al., nor Wang et al., nor Hughes et al. provide the teachings or suggestions that are absent from Carulli et al., Dong et al. and Tamai et al, thus claims 33-36 also are obvious over the references. Again this not found to be persuasive for reasons set forth above with respect to Tamai et al. Therefore, the rejections of record are maintained.

Claim Rejections - 35 USC § 102 (new)

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8a. Claims 8, 9, 30, and 32 are rejected under 35 U.S.C. 102(b) as being anticipated by Rodan et al. (U.S Patent No. 5, 780, 291).

The instant invention is drawn to administering ligands that act on bone density regulating transmembrane receptor to regulate bone strength and treat osteoporosis.

Rodan et al. disclose a human Wnt protein (column1, lines 45-50). It also discloses the role of Wnt in the maintenance of mature osteoblasts and the use of Wnt-x growth factors as a therapeutic agent or in the development of other therapeutic agents to treat bone-related diseases. Therefore meeting the limitations of administering a ligand/effector (Wnt) to regulate bone strength and treat osteoporosis. Thus, claims 8, 9, 30 and 32 are anticipated by Rodan et al.

8b. Claim 30 is rejected under 35 U.S.C. 102(b) as being anticipated by Hastings et al. (U.S Patent No. 5, 780, 263).

The instant invention is drawn to administering ligands that act on bone density regulating transmembrane receptor to treat osteoporosis.

Hastings et al. disclose a CCN-like growth factor (column1, lines 1-10). It also discloses a role for this peptide in the treatment of osteoporosis (column 2, lines 15—22). Therefore meeting the limitations of administering an effector (CCN family member) to treat osteoporosis. Thus, claim 30 is anticipated by Hastings et al.

Claim Rejections - 35 USC § 103 (new)

9a. Claims 30, 33 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rodan et al. (U.S Patent No. 5, 780, 291) in view of Oppermann et al. (U. S. Patent NO. 5, 652, 337).

The teachings of Rodan et al. has been described above in 8a. The teachings of Oppermann et al. have been disclosed in Office Action dated 3/18/2005 and 10/26/05.

Specifically, Oppermann et al. disclose compounds that are capable of targeting BSMR effector to the region of bone remodeling (column 15, lines 38-42). For example, tetracycline and diphosphonates (bisphosphonates) are known to bind to bone mineral, particularly at zones of bone remodeling, when they are provided systemically in a mammal. Accordingly, these molecules may be included as useful agents for targeting OP-3 (a morphogen) to bone tissue.

Alternatively, an antibody or other binding protein that interacts specifically with a surface molecule on the desired target tissue cells also may be used (column 15, lines 38-47).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to treat bone related disorders (osteoporosis) by targeting BSMR effector molecules to regions of bone regeneration or remodeling to modulate bone strength and mineralization as described by Rodan et al. using tetracycline and diphosphonates (bisphosphonates) that are known to bind to bone mineral because Oppermann et al. disclose that tetracycline and diphosphonates (bisphosphonates) are known to bind to bone mineral, particularly at zones of bone remodeling, when they are provided systemically in a mammal. One of ordinary skill in the art would have been motivated to modulate BSMR using a BSMR effector such as Wnt that is targeted to bone producing or remodeling region by compounds such as tetracycline and diphosphonates (bisphosphonates) in order to regulate bone strength and mineralization to treat osteoporosis. Therefore, the instant invention is *prima facie* obvious over Rodan et al. (U.S Patent No. 5, 780, 291) in view of Oppermann et al. (U. S. Patent NO. 5, 652, 337).

9b. Claims 30, 35 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rodan et al. (U.S Patent No. 5, 780, 291) in view of Wang et al. (U. S. Patent NO. 6, 245, 889) and Hughes et al (1995).

The teachings of Rodan et al. (U.S Patent No. 5, 780, 291) has been described above in 8a. The teachings of Wang et al. and Hughes et al. have been described \in the Office Action dated 3/18/2005 and 10/26/05.

Wang et al. disclose the use of BMP-2 and BMP-4 protein may be combined with other agents beneficial to the treatment of the bone and/or cartilage defect, wound, or tissue in question (column 6, lines 65 to column 7, lines 42). These agents include various growth factors such as epidermal growth factor (EGF), platelet derived growth factor (PDGF), transforming growth factors (TGF-α and TGF-β), and insulin-like growth factor (IGF) (column 7, lines 2-5). In addition, these agents may provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells or induce differentiation of progenitors of bone forming cells (column 6, lines 20-23). Wang et al. also teach that for bone and/or cartilage formation, the composition would include a matrix capable of delivering BMP-2, BMP-4 or other BMP proteins to the site of bone and/or cartilage damage (column 7, lines 35-38). It also teaches that BMP-2 may be used individually in a pharmaceutical composition or in combination with BMP-4 and/or one or more of the other BMP proteins (column 7, lines 14-18). Hughes et al. (1995) disclose that the effect of BMPs on nodule formation was seen after only 24 hours of exposure to BMPs. It also teaches that continuous or 24-h exposure to BMP-2 or BMP-4 increased the number of postmitotic ALP-positive cells in log phase culture (abstract).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer another bone morphogenic protein

(BMP) target to regions of bone regeneration or remodeling to modulate bone strength and mineralization as described by Wang et al. using a bone morphogentic protein such as BMP-2 administering BMP-2 at least 24 hrs prior administering the BSMR effector as taught by Hughes et al to increase bone formation because Rodan et al discloses that the administering of Wnt to treat bone-related diseases. Thus, it is possible to affect bone development and to increase or decrease levels of bone mineralization, particularly at zones of bone remodeling, when they are provided systemically in a mammal. One of ordinary skill in the art would have been motivated to treat osteoporosis by administering BMP-2 protein 24 hrs prior to providing BSMR effector that is targeted to bone producing or remodeling region in order to regulate bone strength and mineralization to treat osteoporosis. Further, Hughes teaches that BMP-2 or BMP-4 increased the number of postmitotic ALP-positive cells. Therefore, the instant invention is *prima facie* obvious over Rodan et al. (U.S Patent No. 5, 780, 291) in view of Wang et al. (U. S. Patent NO. 6, 245, 889) and Hughes et al (1995).

10. No claims are allowable.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jegatheesan Seharaseyon, Ph.D whose

telephone number is 571-272-0892. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

JS 05/06

CHRISTINE J. SAOUD
PRIMARY EXAMINER
Christine J. Saoud